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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,108	08/04/2003	Volkhard Lindner	053639-5006-02	6386

23973 7590 08/26/2005

DRINKER BIDDLE & REATH
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EXAMINER	
HADDAD, MAHER M	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 08/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/634,108	LINDNER ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4, 5, 21, 37-44* is/are pending in the application.

4a) Of the above claim(s) *38,40 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,5,21,41 and 42* is/are rejected.

7)☒ Claim(s) *37,39 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/4/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence alignment*.

DETAILED ACTION

1. Claims 4-5, 21, 37-44 are pending.

2. Applicant's election of Group IV by restriction requirement mailed on 6/18/02 in the parent application, 09/692,081, claims 4-5 and 21 (now claims 4-5, 21, 37, 39 and 41-43) directed to an isolated polypeptide of SEQ ID NO:4, filed on 8/4/03, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 38, 40 and 44 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 4-5, 21, 37, 39 and 41-43 are under examination as they read on an isolated polypeptide of SEQ ID NO:4.

5. The specification on page 1 should be amended to reflect the status of 09/692,081 and the relationship between 09/692,081 and the instant application.

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Page 31, line 4 and 17 contains embedded hyperlinks and/or other forms of browser-executable code which are impermissible and require deletion.

7. Applicant's IDS, filed 8/4/03, is acknowledged.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 4-5, 21 and 41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide comprising REMODEL polypeptide of SEQ ID NO: 4, a composition thereof and a chimeric polypeptide thereof covalently linked to a tag polypeptide; does not reasonably provide **enablement** for any isolated polypeptide comprising any "mammalian REMODEL" in claim 4, wherein said mammalian REMODEL molecule shares "at least about 6% sequence identity" with an amino acid sequence of SEQ ID NO: 4 in claim 5, or a composition thereof in claim 21, or an isolated chimeric polypeptide, said chimeric polypeptide comprising a tag polypeptide covalently linked to any "mammalian REMODEL polypeptide in claim 41". The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

Besides the rat REMODEL polypeptide of SEQ ID NO: 2 and 5 and the human REMODEL polypeptide of SEQ ID NO: 4, the specification fails to establish the structure of any mammalian REMODEL. "REMODEL" is an arbitrary protein name. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of REMODEL polypeptides (human, mouse, rat, among other species) broadly encompassed by the claims.

The specification does not provide a sufficient enabling description of the claimed invention. The specification discloses only rat and human REMODEL polypeptide sequences (SEQ ID NO:2 and 4) encoded REMODEL nucleic acid sequences (SEQ ID NO:1 and 3 respectively), and the amino acid sequence of the long form of rat REMODEL (rREMODEL$_L$) (SEQ ID NO: 5) encoded by SEQ ID NO: 1, with a disclosed activity such as developing bone and regulating calcification (e.g., page 122 at lines 1-5). The instant claims encompass in their breadth *any* amino acid sequence of mammalian REMODEL, wherein the amino acid sequence of REMODEL " shares at least about 6% sequence identity of SEQ ID NO: 4"; a composition thereof or a chimeric polypeptide thereof.

However, there does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the various amino acids recited in the instant claims. A person of skill in the art would not know which sequences are essential, which sequences are non-essential, and what particular sequence lengths identify essential sequences. There is insufficient guidance to direct a person of skill in the art to select particular sequences or sequence lengths as essential for REMODEL activity. Without detailed direction as to which amino acid sequences are essential to the function of the human REMODEL polypeptide, a person of skill in the art would not be able to determine without undue experimentation which of the plethora of amino acid sequences encompassed by the instant claims would share the activity of REMODEL polypeptide of SEQ ID NO:4, other than amino acid of SEQ ID NO:4.

The art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases and recognized that it was unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences. Attwood (Science 2000; 290:471-473) teaches that "[i]t is presumptuous to make functional assignments merely on the basis of some degree of similarity between sequences. Similarly, Skolnick et al. (Trends in Biotech. 2000; 18(1):34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall

structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Thus it is unpredictable if any functional activity will be shared by two polypeptides having less than 100% identity over the full length of their sequences.

The specification does not provide sufficient teaching as to how it can be assessed that treatment of said diseases was achieved after the administration of the therapeutic composition of the invention.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

10. Claims 4-5, 21 and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an isolated polypeptide comprising REMODEL polypeptide of SEQ ID NO: 4, a composition thereof and a chimeric polypeptide thereof covalently linked to a tag polypeptide.

Applicant is not in possession of any isolated polypeptide comprising any "mammalian REMODEL" in claim 4, wherein said mammalian REMODEL molecule shares "at least about 6% sequence identity" with an amino acid sequence of SEQ ID NO: 4 in claim 5, or a composition thereof in claim 21, or an isolated chimeric polypeptide, said chimeric polypeptide comprising a tag polypeptide covalently linked to any "mammalian REMODEL polypeptide in claim 41".

Neither the exemplary embodiments nor the specification's general method appears to describe structural features, in structural terms, that are common to the genus. That is, the specification provides neither a representative number of species (mammalian REMODEL) to describe the claimed genus, nor does it provide a description of structural features that are common to species (REMODEL molecule). The specification provides no structural description of mammalian REMODEL other than rat REMODEL of SEQ ID NOs: 2 and 5 and human REMODEL of SEQ ID NO: 4; in essence, the specification simply directs those skilled in the art to go figure out for themselves what the claimed polypeptide looks like. The specification's disclosure is inadequate to describe the claimed genus of polypeptides that "share at least about 6% sequence identity" of a "mammalian REMODEL".

Applicant has disclosed only amino acid of SEQ ID NOs: 2, 4 and 5; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the

structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e1) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

35 U.S.C. § 102(e), as revised by the AIPA and H.R. 2215, applies to all qualifying references, except when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. For such patents, the prior art date is determined under 35 U.S.C. § 102(e) as it existed prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. § 102(e)).

12. Claim 4-5, 21 and 41-42 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 00/52151 (10/09/00).

13. Claim 4-5, 21 and 41-42 are rejected under 35 U.S.C. 102(e1) as being anticipated by WO 00/52151 (10/09/00).

The WO `151 publication teaches a 278 amino acid sequence (HSECP-5) comprising 100% sequence identity with an amino acid sequence of SEQ ID NO: 4 (see attached sequence alignment, published SEQ ID NO: 5, published claims 1-2 and 15 in particular). The `151 publication further teaches a potential signal peptides of published SEQ ID NO: 5 present at amino acids M1-A65 (see table 2, row 6 in particular). Furthermore, the `151 publication teaches a composition comprising published SEQ ID NO: 5 and a pharmaceutically acceptable excipients (see published claim 15 in particular). Further, The `151 publication teaches a chimeric HSECP protein containing a heterologous moiety that can be recognized by a commercially a vailable antibody such as glutathione S-transferase (GST), maltose binding protein (MBP),6-His, FLAG, c-myc and hemagglutinin (HA) (see page 31, line 29 through page 32, line 11 in particular). Further, while claim 42, recites the term "consists of", the amino acids M1-A35 of published SEQ ID NO: 5, is considered a tag polypeptide covalently linked to a mammalian REMODEL polypeptide consists of claimed SEQ ID NO: 4. It is noted that the specification on page 40, lines 17-20, defined "tag" polypeptide is meant any protein which, when linked by a peptide bond to a protein of interest, may be used to localize the protein, to purify it from a cell extract, to immobilize it for use in binding assays, or to otherwise study its biological properties and/or function.

The reference teachings anticipate the claimed invention.

14. No claim is allowed.

15. Claim 37 is objected because it recites non-elected embodiments, but would be allowable if rewritten to include only the elected embodiment. Further, claim 39 is objected to as being dependent upon a objected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

16. Claim 43 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

August 22, 2005

Maher Haddad

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600

```
CC   endometrium, oesophagus, kidney, larynx, liver, lung, omentum, ovary,
CC   pancreas, rectum, thyroid, myometrium, prostate, skin, small intestine,
CC   bladder, spleen or stomach.
XX
SQ   Sequence 243 AA;

  Query Match           100.0%;  Score 1303;  DB 8;  Length 243;
  Best Local Similarity  100.0%;  Pred. No. 9e-121;
  Matches  243;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MRPQGPAASPQRLRGLLLLLLLQLPAPSSASEIPKGKQKAQLRQREVVDLYNGMCLQGPA 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MRPQGPAASPQRLRGLLLLLLLQLPAPSSASEIPKGKQKAQLRQREVVDLYNGMCLQGPA 60

Qy         61 GVPGRDGSPGANGIPGTPGIPGRDGFKGEKGECLRESFEESWTPNYKQCSWSSLNYGIDL 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GVPGRDGSPGANGIPGTPGIPGRDGFKGEKGECLRESFEESWTPNYKQCSWSSLNYGIDL 120

Qy        121 GKIAECTFTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECSGPLPIEAIIYLDQ 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 GKIAECTFTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECSGPLPIEAIIYLDQ 180

Qy        181 GSPEMNSTINIHRTSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNSVSRIIIEE 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 GSPEMNSTINIHRTSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNSVSRIIIEE 240

Qy        241 LPK 243
              |||
Db        241 LPK 243


RESULT 13
AAB08856
ID   AAB08856 standard; protein; 278 AA.
XX
AC   AAB08856;
XX
DT   15-JAN-2001  (first entry)
XX
DE   Amino acid sequence of a human secretory protein.
XX
KW   Human; secretory protein; HSECP; cancer; gastrointestinal disorder;
KW   inflammation; cardiovascular disorder; neurological disorder.
XX
OS   Homo sapiens.
XX
FH   Key             Location/Qualifiers
FT   Peptide         1. .65
FT                   /note= "signal sequence"
FT   Modified-site   7
FT                   /note= "potential phosphorylation site"
FT   Modified-site   64
FT                   /note= "potential phosphorylation site"
FT   Modified-site   132
FT                   /note= "potential phosphorylation site"
FT   Modified-site   179
FT                   /note= "potential phosphorylation site"
FT   Modified-site   221
FT                   /note= "potential glycosylation site"
FT   Modified-site   230
FT                   /note= "potential phosphorylation site"
FT   Modified-site   252
FT                   /note= "potential phosphorylation site"
XX
PN   WO200052151-A2.
XX
PD   08-SEP-2000.
XX
PF   03-MAR-2000; 2000WO-US005621.
XX
PR   05-MAR-1999;   99US-0123117P.
XX
PA   (INCY-) INCYTE PHARM INC.
XX
PI   Tang YT, Lal P, Baughn MR, Yue H, Au-Young J, Lu DAM, Azimzai Y;
XX
DR   WPI; 2000-579282/54.
DR   N-PSDB; AAA75110.
XX
PT   Twenty two human secretory proteins for diagnosing, treating and
PT   preventing cancer, inflammation, and gastrointestinal, cardiovascular and
PT   neurological disorders.
XX
PS   Claim 1; Page 83; 107pp; English.
XX
CC   The present sequence represents a human secretory protein, designated
CC   HSECP-1. The specification also describes HSECP-2 to HSECP-22. The
CC   proteins are useful for diagnosing, treating and preventing cancer,
CC   inflammation, and gastrointestinal, cardiovascular and neurological
CC   disorders. The proteins may also be used to identify agonists,
CC   antagonists, and inhibitors. The polynucleotides may be used for
CC   producing the protein recombinantly, and as a source of probes and
CC   primers for isolating and identifying related sequences
XX
SQ   Sequence 278 AA;

  Query Match           100.0%;  Score 1303;  DB 3;  Length 278;
  Best Local Similarity  100.0%;  Pred. No. 1.1e-120;
  Matches  243;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MRPQGPAASPQRLRGLLLLLLLQLPAPSSASEIPKGKQKAQLRQREVVDLYNGMCLQGPA 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         36 MRPQGPAASPQRLRGLLLLLLLQLPAPSSASEIPKGKQKAQLRQREVVDLYNGMCLQGPA 95

Qy         61 GVPGRDGSPGANGIPGTPGIPGRDGFKGEKGECLRESFEESWTPNYKQCSWSSLNYGIDL 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         96 GVPGRDGSPGANGIPGTPGIPGRDGFKGEKGECLRESFEESWTPNYKQCSWSSLNYGIDL 155

Qy        121 GKIAECTFTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECSGPLPIEAIIYLDQ 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        156 GKIAECTFTKMRSNSALRVLFSGSLRLKCRNACCQRWYFTFNGAECSGPLPIEAIIYLDQ 215

Qy        181 GSPEMNSTINIHRTSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNSVSRIIIEE 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        216 GSPEMNSTINIHRTSSVEGLCEGIGAGLVDVAIWVGTCSDYPKGDASTGWNSVSRIIIEE 275

Qy        241 LPK 243
              |||
Db        276 LPK 278


RESULT 14
AAM25746
ID   AAM25746 standard; protein; 278 AA.
XX
AC   AAM25746;
XX
DT   16-OCT-2001  (first entry)
XX
DE   Human protein sequence SEQ ID NO:1261.
XX
KW   Human; cancer; ulcer; HIV infection; human immunodeficiency virus;
KW   antiinflammatory; antirheumatic; antiarthritic; immunosuppressive;
KW   antibacterial; endocrine; cardiant; central nervous system; virucide;
KW   anti-HIV; fungicide; antimutagen; cardiovascular; antianaemic; anaemia;
KW   antiaggregant; haemostatic; vulnerary; antiulcer; osteopathic; eczema;
KW   dermatological; antiallergic; antiasthmatic; antidiabetic; cytostatic;
KW   neuroprotective; antidepressant; nootropic; antiparkinsonian; infection;
KW   immunostimulant; gene therapy; antisense therapy; vaccine; inflammation;
KW   antianaphylactic; rheumatoid arthritis; septic shock; pancreatitis;
KW   cardiac dysfunction; neuropathology; cardiac anaphylaxis; autoimmunity;
KW   genetic disease; haematopoietic disorder; platelet disorder; asthma;
KW   thrombocytopaenia; osteoporosis; severe combined immunodeficiency;
KW   allergic rhinitis; diabetes; multiple sclerosis; depression;
KW   Alzheimer's disease; Parkinson's disease; neurodegenerative disorder;
KW   neurological disorder.
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